Inhalational Anthrax and Smallpox: Lessons Learned: 2001 Anthax Attacks and 2003 Smallpox Preparedness Program

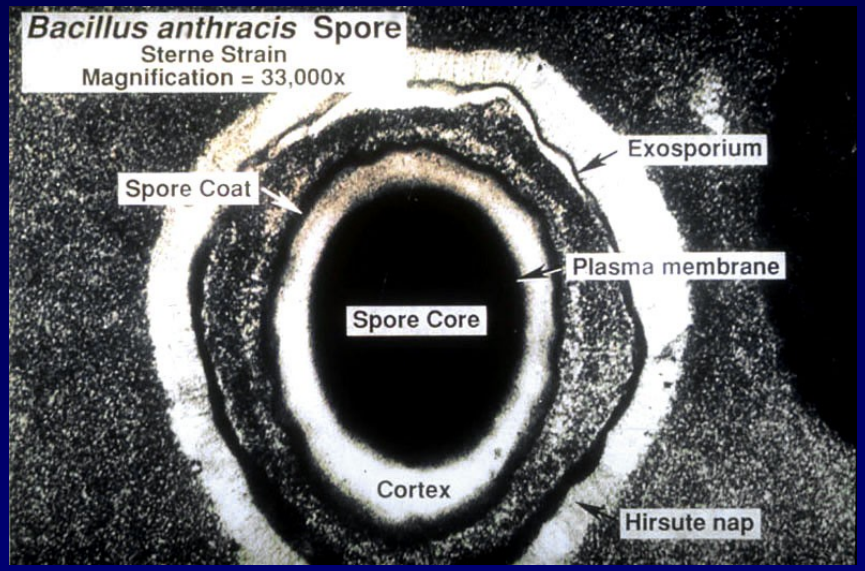
Global Medicine Course

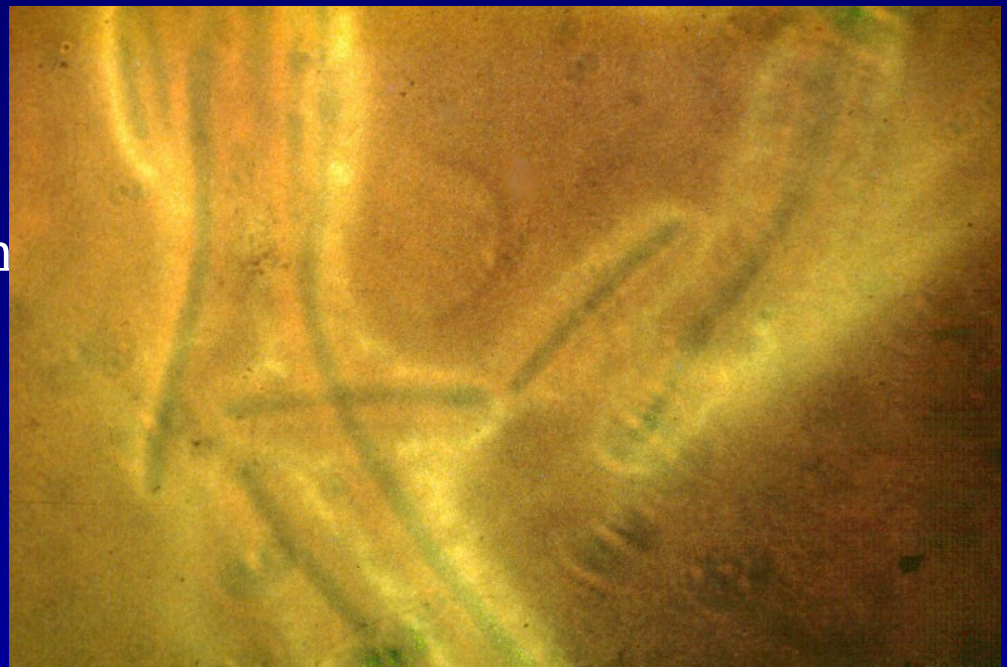
USAF School of Aerospace Medicine

10 Feb 2004

Bacillus anthracis

- Non-motile spore forming gram-positive bacillus
- Virulence factors :
  - **Polyglutamic acid capsule**
  - **Toxin**
    - Protective antigen
    - Edema factor
    - Lethal factor





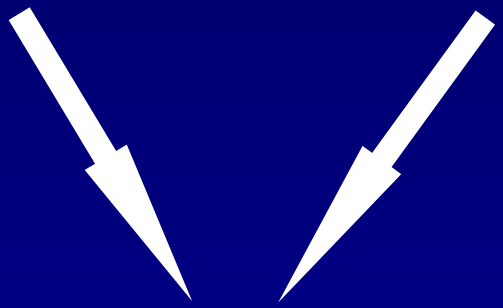
Anthrax Toxin Components

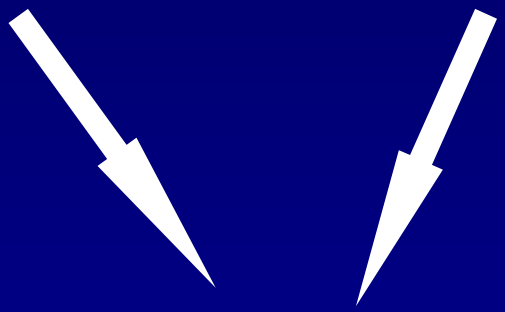
Activities, Properties, Nomenclature

Edema Factor (EF)
MW 89,000
Adenylate Cyclase

Protective Antigen (PA)
MW 83,000

Lethal Factor (LF)
MW 90,000
? Metallo-protease





Edema Toxin

Increased Cyclic AMP

Lethal Toxin

Macrophage Lysis

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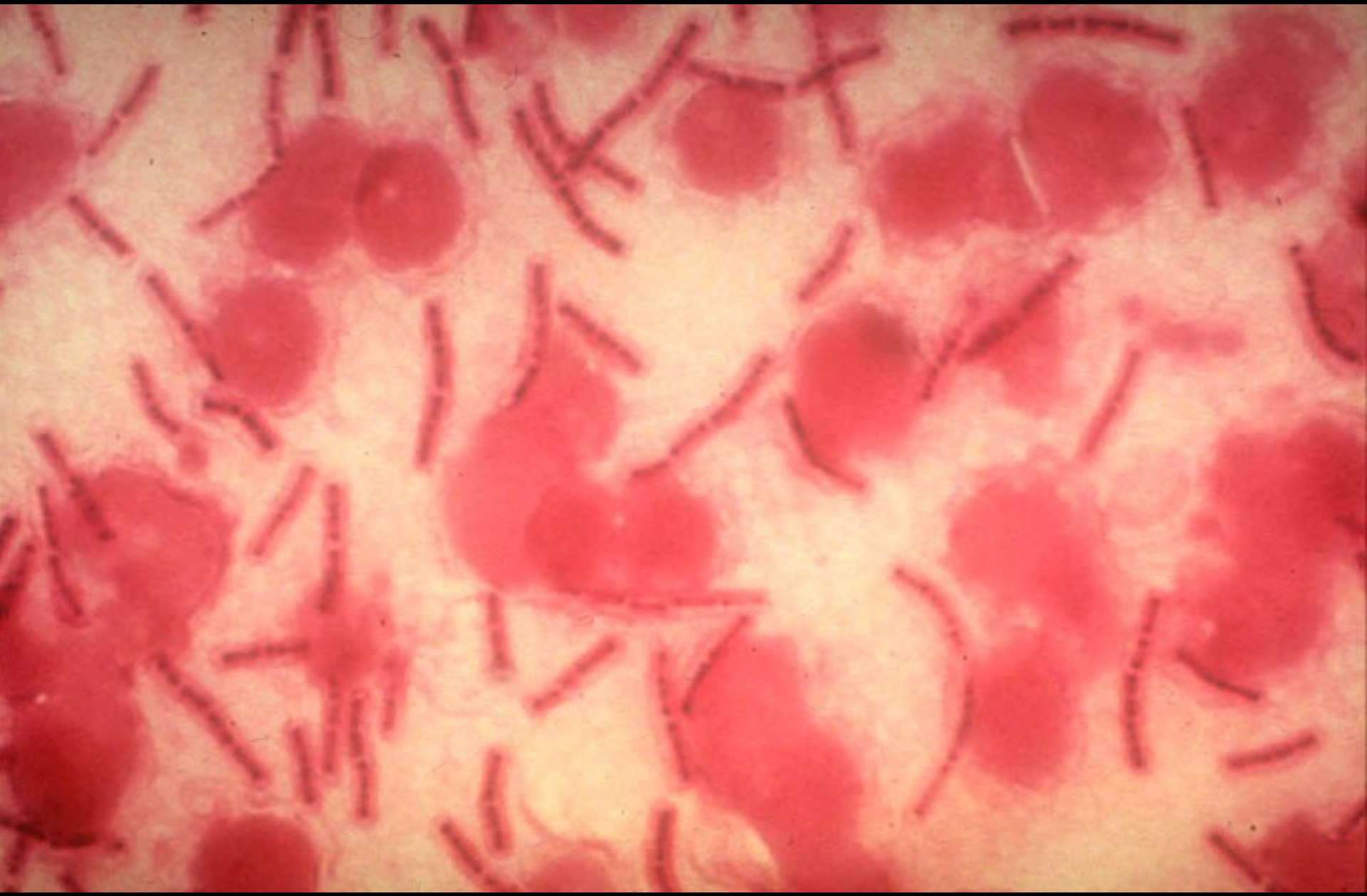
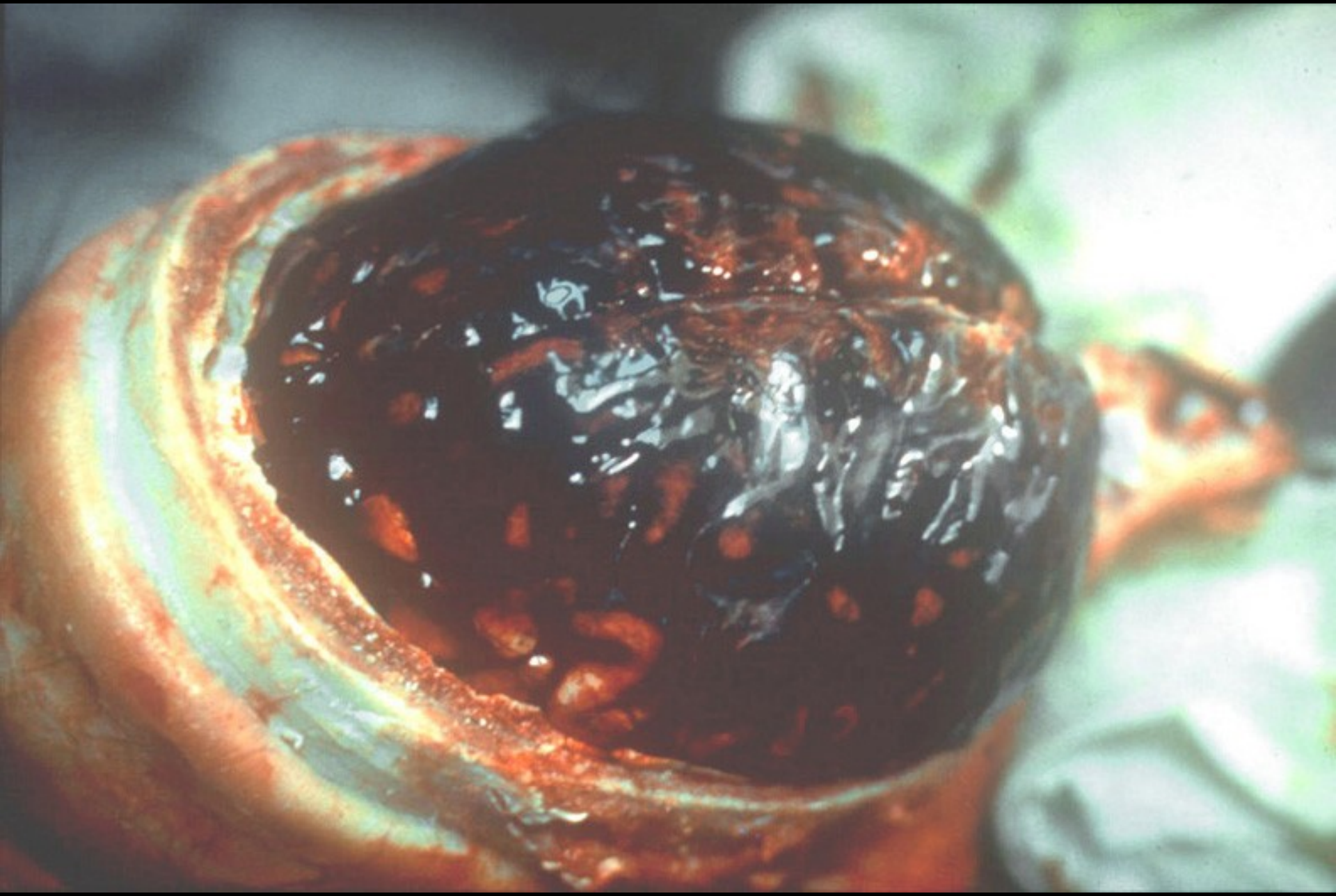




Autopsy Findings: Sverdlovsk, 1979

- Inhalation Anthrax
  - **Hemorrhagic necrosis of thoracic lymph nodes 42/42**
  - **Hemorrhagic mediastinitis 42/42**
  - **Focal hemorrhagic necrotizing pneumonia 11/42**
- Metastatic infection
  - **Multiple gastrointestinal submucosal lesions 39/42**
  - **Hemorrhagic meningitis 21/42**
- Microbiology
  - ***B. anthracis* identified by tissue culture in 20/42**
  - ***B. anthracis* identified by histology 35/42**
  - **PCR analysis of tissue from 11 victims demonstrated DNA from at least 4 different virulent *B. anthracis* strains and vaccine**

- **Abramova et al. *Proc Natl acad Sci USA* 1993;90:2291-4**
- **Jackson et al. *Proc Natl Acad Sci USA* 1988;95:1224-9**

Symptoms: 11 Inhalational Anthrax Bioterror Casualties, Oct-Nov 2001

Fever	11	Cough	10
Fatigue, malaise	11	Dyspnea	8
Chills	10	Chest pain	7
Myalgias	7	Nausea or Vomiting	9
Sweats	7	Abd pain	3
Sore throat	2	Headache	5
Rhinorrhea	1	Confusion	4

Emer Infec Dis 2001;7:933-944

MMWR 2001;50:1049-1051

Clinical Findings: 10 Inhalational Anthrax Bioterror Casualties 2001

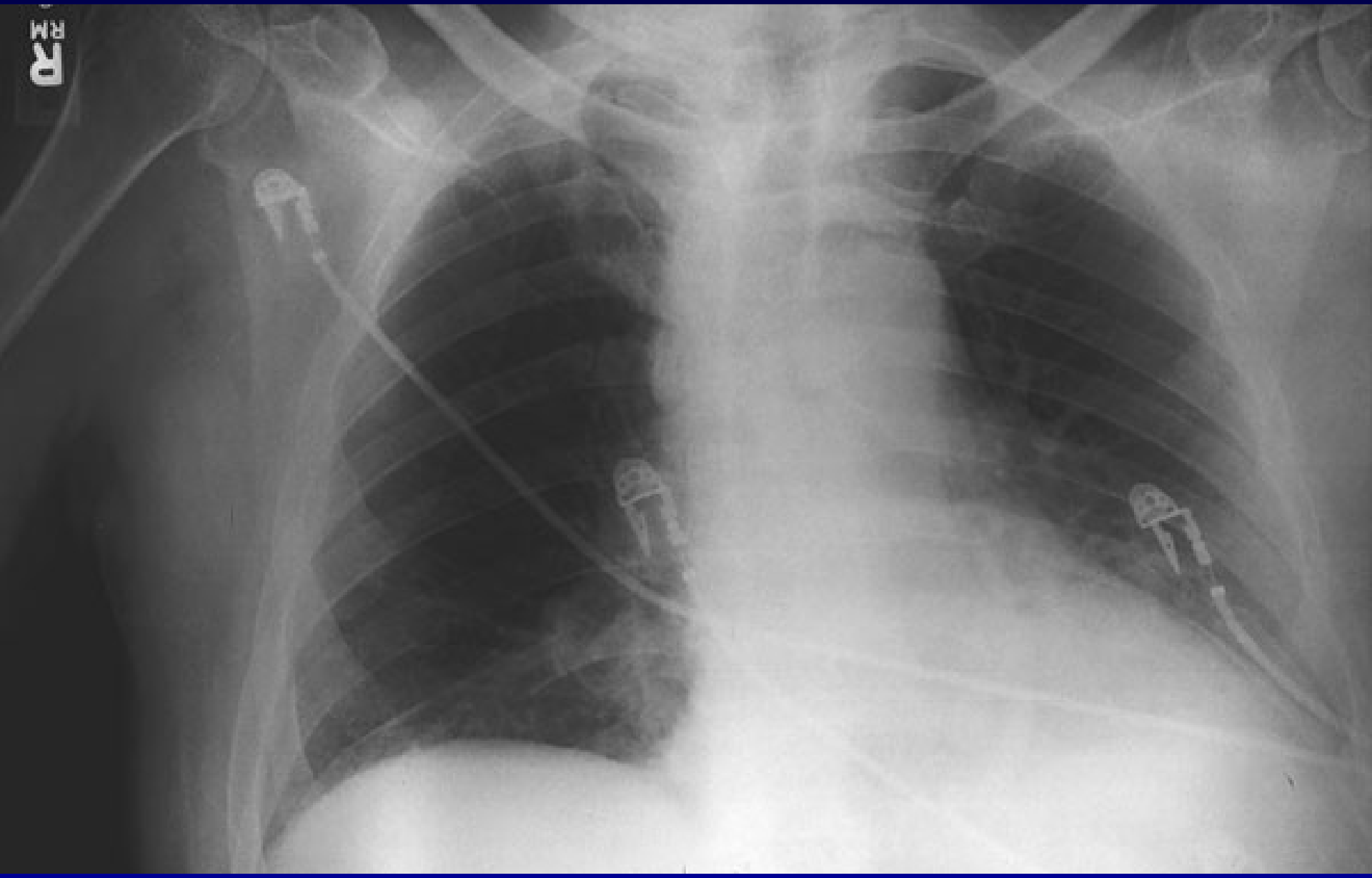
Fever (> 37.8° C) 8
Tachycardia (> 100) 9
Hypotension 1
Hypoxemia 7
(A-a > 30 mm/Hg)
(Hg O2sat < 94%)

ALT/AST > 40 9
WBCat presentation 9,800 (7.5-13,300)
PMN > 70% 7
WBC 26,400 throughout course (11,900-49,600)

Emer Infec Dis 2001;7:933-944
MMWR 2001;50:1049-1051

Sx/Sx	Ant	Flu	ILI
Elevated Temperature	70 %	68-77%	40-73%
Fever or chills	100	83-90	75-89
Fatigue/Malaise	100	75-94	62-94
Nonproductive cough	90	84-93	72-80
Headache	50	84-91	74-89
Myalgias	50	67-94	73-94
Abd pain	30	22	22
Nausea or Vomiting	80	12	12
Chest discomfort		35	23

MMWR 2001;50:984-6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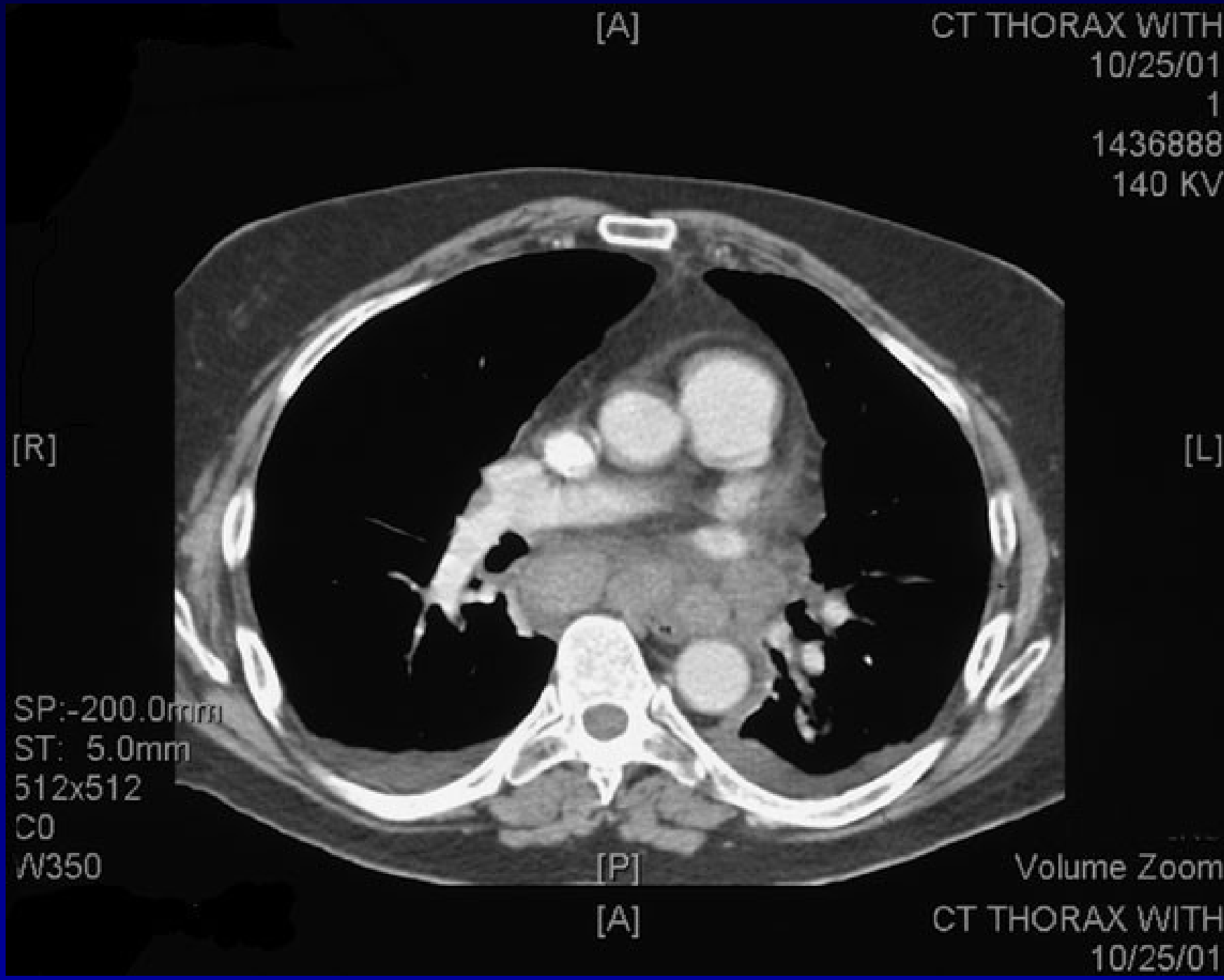
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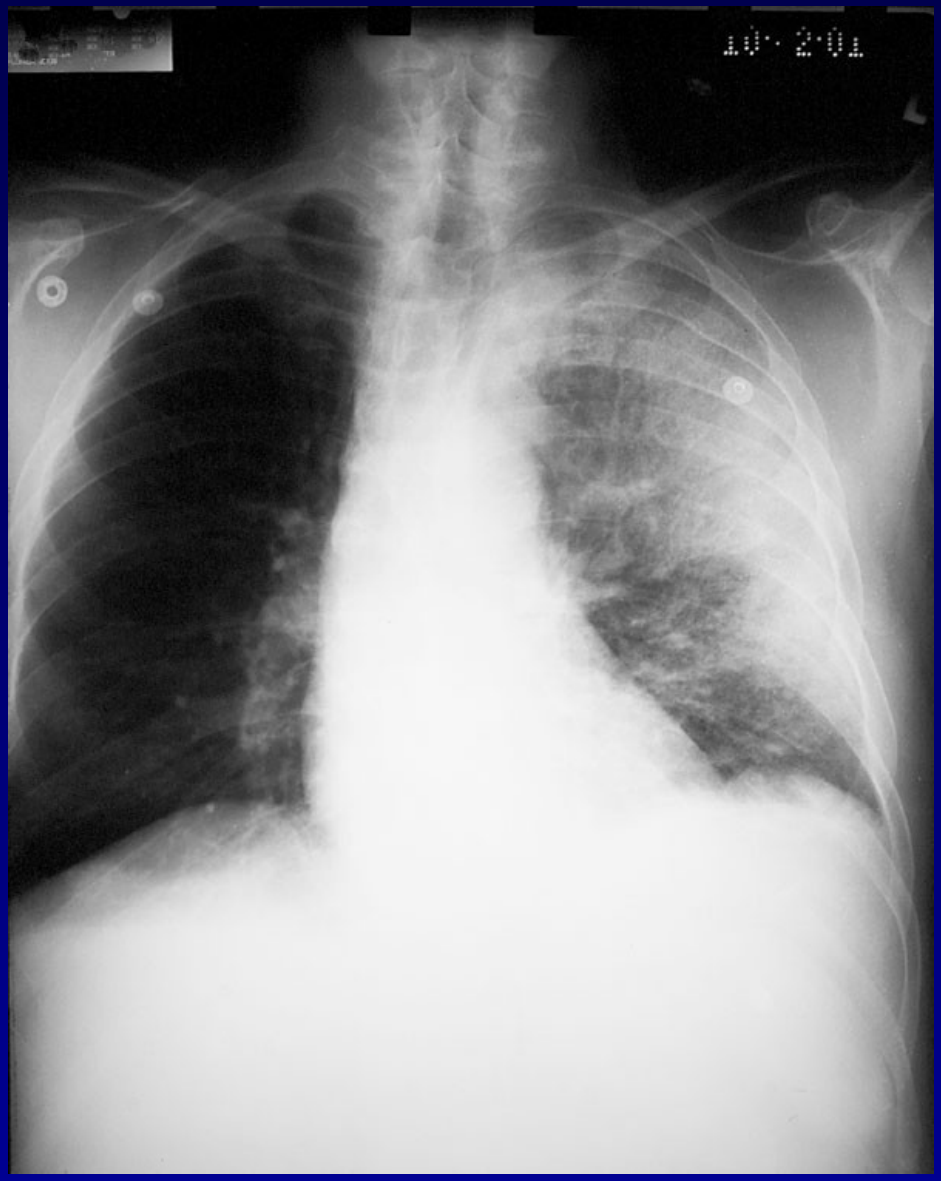

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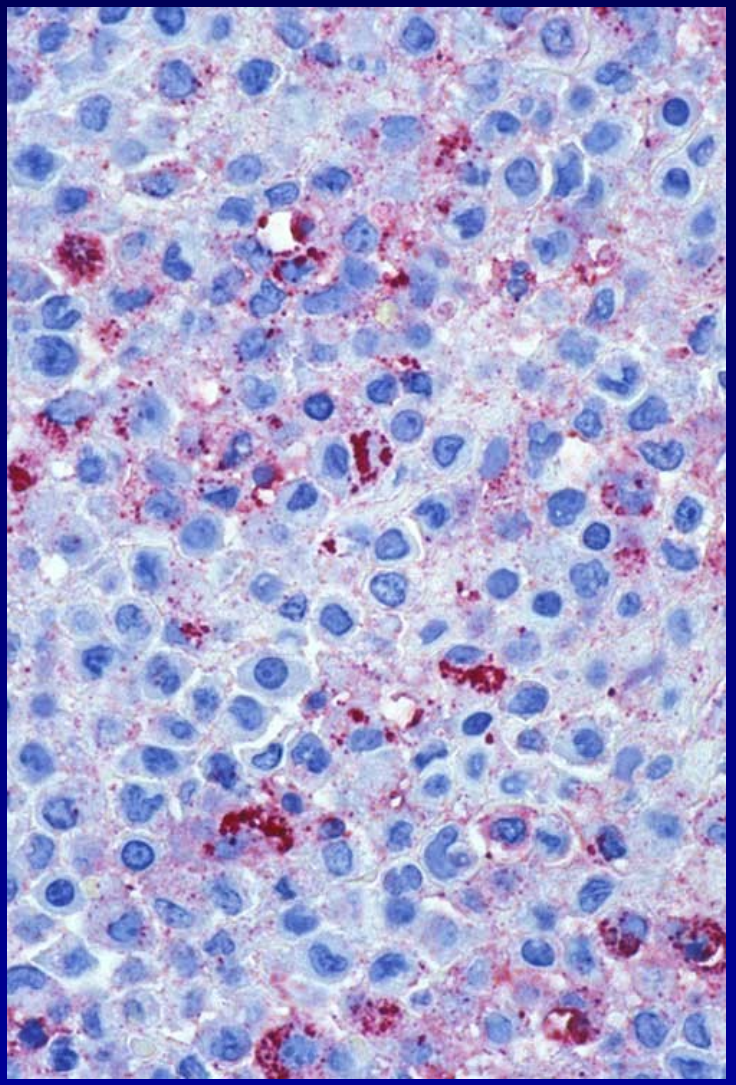
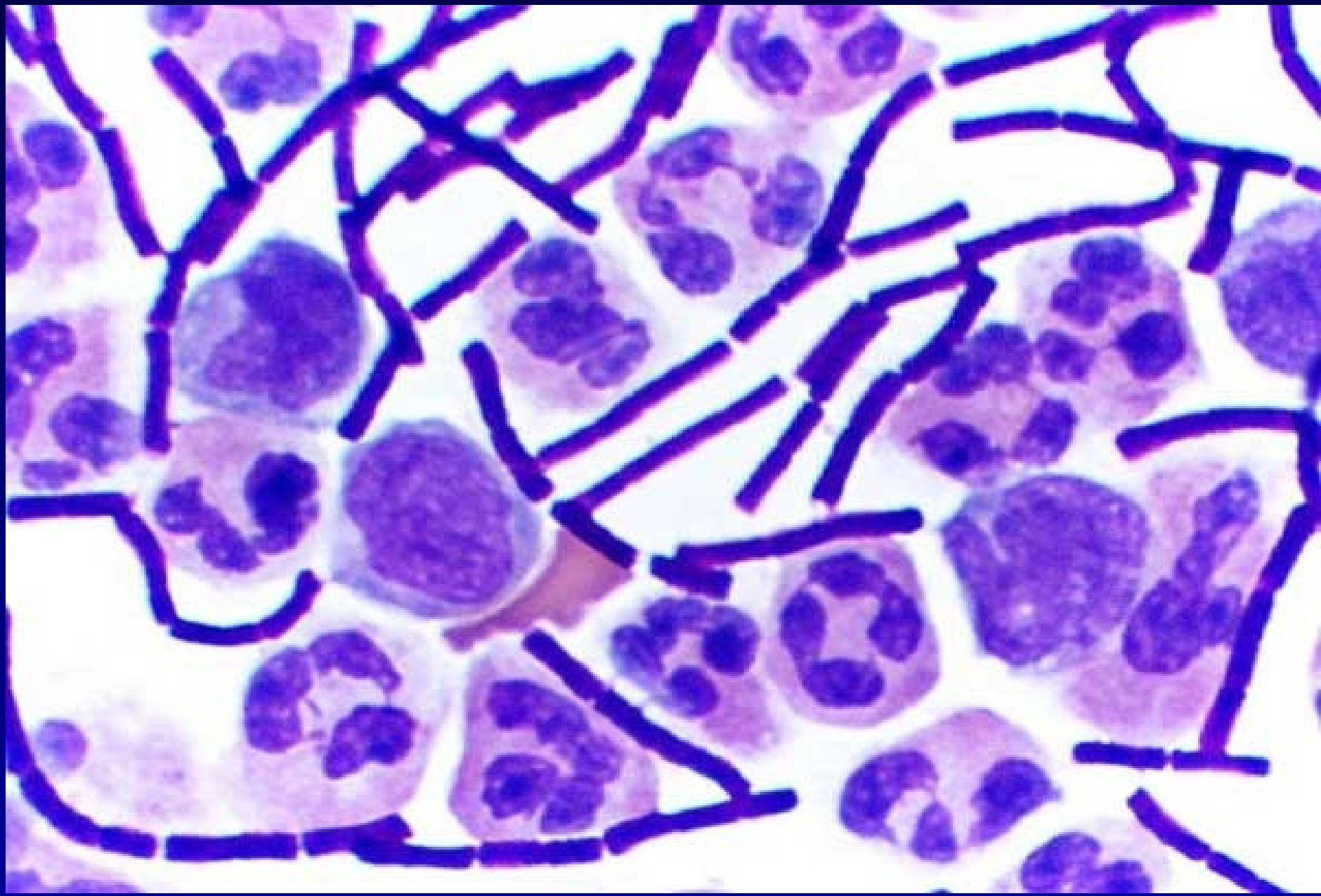
W:1600 L:-550
P 180

Pleural Effusions

- Occurred in all cases
- 8/11 on presentation
- Small on presentation but progressed
- Hemorrhagic
- RBC 73,000-244,000
- Protein 2.6-4.2 g/dL
- WBC 286-3,000/mm3
- Thoracentesis in 7/10
- Chest tube: 3/7





Laboratory Diagnosis

- Blood cultures
  - Highly sensitive if taken before antibiotic Rx
  - Negative if taken after antibiotic Rx begun
- Buffy coat smear
  - Potentially useful in cases presenting in late stage
- Pleural fluid, pleural bx, transbronchial bx- culture, FA, PCR
- CSF gram stain, culture, FA, PCR
- Nasal swab: Culture
  - May identify cases previously started on antibiotic Rx

Rx: Inhalational, Gastrointestinal, Oropharyngeal Anthrax

MMWR 2001;50:909-919

Ciprofloxacin 400 mg (10-15 mg/kg) IVq 12 hour

OR

Doxycycline 100 mg (2.2mg/kg) IV q 12 hours

PLUS one or two additional antimicrobials:

Rif, vanco, clinda, PCN, AMP, IMP, chloro, clarithro

(cip/rif/vanco or cip/rif/clinda)

P improvement: may narrow to one or two drugs; PO when clinically appropriate to complete 60 day course

?Role of corticosteroids: severe edema, meningitis

Treatment of Cutaneous Anthrax

MMWR 2001;50:909-919

- Adults:
  - Ciprofloxacin 500 mg PO BID x 60 days
  - Doxycycline 100 mg PO BID x 60 days
  - Amoxicillin 500 mg PO TID p initial improvement, for sensitive strain, to complete course of Rx
- Children
  - Ciprofloxacin 10-15 mg/kg PO q 12 hrs (< 1 gm/d)
  - Doxycycline
    - **> 8 yrs/45 kg: 100 mg PO q 12 hr**
    - **≤ 8 yrs and ≤ 45 kg: 2.2 mg/kg PO q 12 hr**
  - Amoxicillin 500 mg TID or 80 mg/kg/day in divided TID doses p initial improvement, for sensitive strain

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm

Postexposure Prophylaxis

- Adults:
  - Ciprofloxacin 500 mg PO BID x 60 days
  - Doxycycline 100 mg PO BID x 60 days
  - Amoxicillin 500 mg PO TID after identification of sensitive strain, to complete course of Rx
    - **Option 1: additional 1-40 days antibiotic**
    - **Option 2: additional 1-40 days plus 3 doses AVA**
- Children
  - Ciprofloxacin 10-15 mg/kg PO q 12 hrs (< 1 gm/d)
  - Doxycycline
    - $\leq$ 8 yrs and $\leq$ 45 kg: 2.2 mg/kg PO q 12 hr
    - Amoxicillin 500 mg TID or 80 mg/kg/day in divided TID doses for sensitive strain

Adherence to PEP: 2001

Site	N	10 days	30 days	60 days
Florida	1,082	81 %	40 %	78 %
NJ	1,402	25	64	76
DC-Capitol	600	n/a	59	82
DC-Postal	2,743	60	45	62
NYC	2,259	n/a	23	58
CT	1,217	n/a	n/a	69

Shepard et al. *Emerg Infect Dis* 2002; 8:1124-32

Adverse Events

	Day 10			Day 30		
Drug	cip	dox		cip	dox	
N (#)	2,446	165	p	737	2,050	p
> 1 SE	45 %	49 %	0.27	77 %	71 %	<0.01
GI	26	26	0.89	42	49	<0.01
CNS	18	11	0.08	23	18	0.01
Derm	7	7	0.8	14	14	0.6

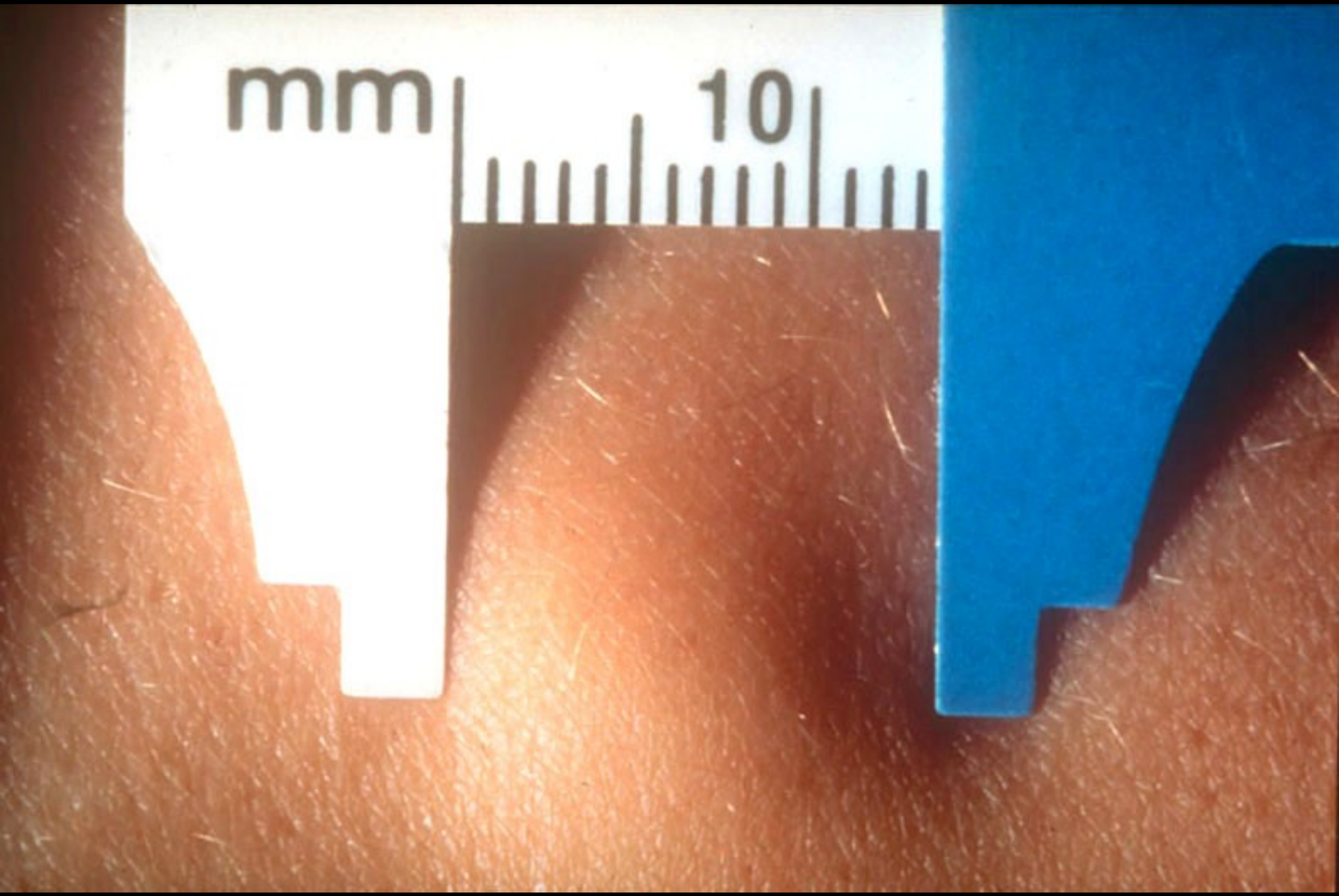
Shepard et al, *Emerg Infect Dis* 2002;8:1124-32

Anthrax Vaccines

- Attenuated spore vaccine
  - Nonencapsulated, toxigenic strain
  - Veterinary use
  - Human use- Eastern Europe
  - Cellular>>humoral responses vs wide range of bacterial antigens
  - Reactogenicity
- Protective Antigen (PA) vaccine
  - Humoral response vs. PA (toxin component)

Animal Models

- Nonhuman Primates
  - Immunized at 0 and 2 weeks:aerosol challenge (Salisbury Med Bull (Suppl) 1995;87:127-8)
    - 8 weeks: 255-760 LD 50 10/10 survived
    - 38 weeks: 161-247 LD 50 3/3 survived
    - 100 weeks: 239-535 LD 50 7/8 survived
  - Immunized at 0 and 4 weeks: aerosol challenge (Salisbury Med Bull (Suppl)1995;87:130)
    - 3 months : 837-951 LD50 9/9 survived
  - 5 of 5 immunized at 0 and 4 weeks survived aerosol challenge (USAMRIID, unpublished data)
  - 10 of 10 immunized once survived aerosol challenge (93 LD50) at 6 weeks (Vaccine 1998;16:1141)
  - total: 44 of 45 (98%) survived
  - 14 of 14 controls died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Injection-Site Reactions After Anthrax Vaccination

- **For both genders, most injection-site reactions resolve in 1-3 days**
- **From Hawaii, Korea, Ft. Bragg, Ft. Detrick, 1993-**

  2000: Redness, itching, swelling (lasting a few days)

  - **Less than 1 inch: men up to 30%, women up to 60%**
  - **1 to 5 inches: 1% to 5%**
  - **Greater than 5 inches: 1%**
  - **Swelling may extend below elbow**
  - **Soreness or local pain in 8% to 19%**
  - **Lump: 30% to 90% (may persist several**

Risks: Vaccine
(CDC Dec 2001)

18 safety studies

Local reactions: soreness, redness, itching, swelling

- 30% of men, 60% of women
- Lump at site occurs commonly and lasts a few weeks

Systemic reactions:

- Rashes (16%), headaches (14% to 25%), malaise (6% to 17%), muscle aches (3% to 34%), fever (1% to 5%).
- Typically resolve in a few days

Rare reactions:

- Severe allergic reactions < 1 per 100,000 doses

Contraindications, Warnings, and Precautions

- Contraindications
  - Severe reaction to a previous dose
  - Previous case of cutaneous anthrax
- Warnings
  - Pregnancy category C; breast feeding not contraindicated
  - Active infection: defer dose
  - Corticosteroid or other immunosupressive Rx: dose should be delayed. If therapy is long term, an extra dose should be given a month or more after Rx discontinued
- Precautions
  - Should be administered only to healthy men and women ages 18-65

Injection-Site Reactions and Systemic Events

- **Screen for previous adverse reactions**
- **Treat and pre-treat adverse events**

  See clinical guidelines on www.vhcinfo.org
- **Do not give next dose if side effects persist from previous vaccination**
- **Issue temporary exemption if symptoms persist**
- **Consult provider skilled in diagnosis and management of vaccine adverse events for permanent exemption**

Emerging Issues: Antibiotic Resistant Attenuated Vaccine STI-AR

Drug	MIC (µg/ml)	Mechanism
Ampicillin	512	PCN-ase
Rifampin	128	Mutant-STI-PR
Doxycycline	64	*tet*
Chloramphenicol	64	*cat*
Macrolides, Lincomycin	128	ermC

Pomerantsev et al. *Salisbury Med Bull* 1996; Special Suppl 87:130-1

Emerging Issues

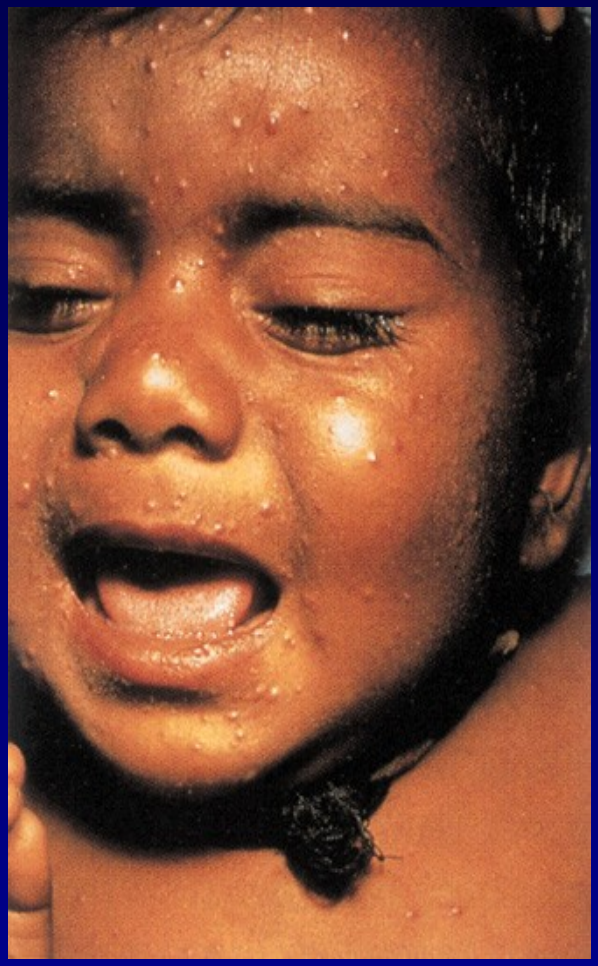
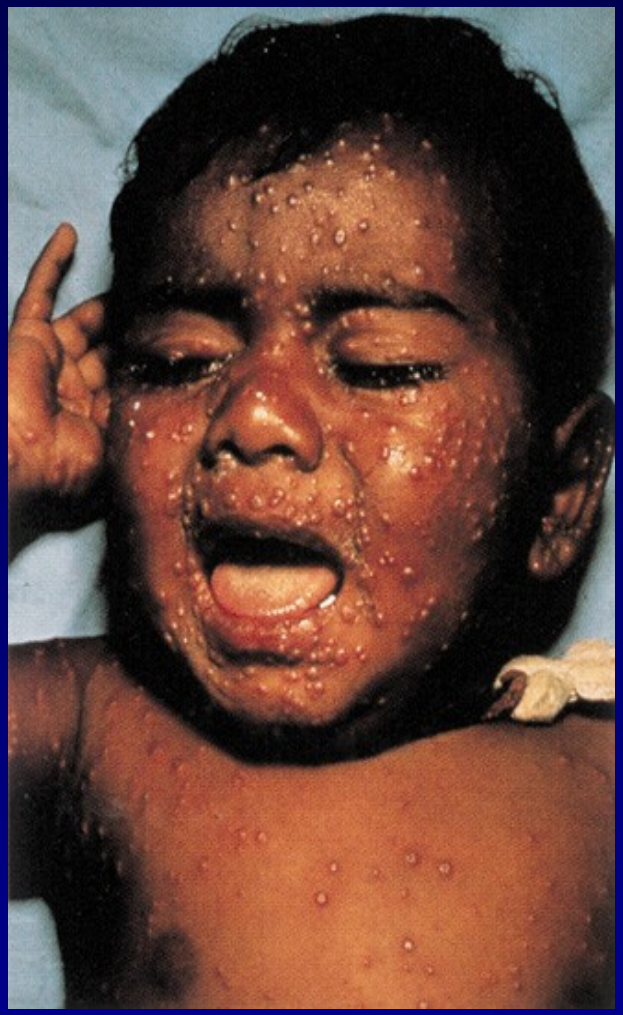
- Genetically engineered *B. anthracis*
  - **Expression of cereolysin AB genes (hemolysin)**
  - **Defeats attenuated spore vaccine in hamster model**
  - **Disease prevented by same genetic modifications in attenuated spore vaccine**
  - **Not tested vs. PA vaccine**
    - **Different vaccines/immunologic responses**
    - **Need empiric study**
      - **Salisbury Med Bull 1996 Special Suppl 87:130-131**
      - **Vaccine 1997;15:1846-1850**

AVA: New Issues

- Simplified dosing schedule
  - **Human data:**
    - **Seroconversion after 2 doses**
    - **Amnestic response following boosting 18-24 months after 2 initial doses**
  - **Animal data:**
    - **Protected vs. aerosol challenge 2 years after 2 initial doses**
- IM vs. SQ dosing
  - **Immunogenic, less reactogenic in pilot study**
- Study in progress: Immunogenicity of simplified dosing regimen (0, 4wks, 6, 12, and 18 months), IM vs. SQ

Directions for Future Research

- Recombinant PA
  - ***B. anthracis* modified to express PA gene; no LE, LF**
  - **Can simplify manufacturing process**
- DNA plasmid vaccine
  - **Codes for PA**
  - **Effective in mouse model (*Vaccine* 1999;17:340-4)**
- Anthrax immune globulin
- Nonspecific immune enhancement:
  - **Gene therapy: Up-regulation of IL-12**

Surveillance and Containment: Case Definitions

CDC 2003: Smallpox Plan and Guidelines

- International emergency-immediate report to command and public health authorities
- Clinical Case Definition: Illness c acute fever ≥ 101° F (38.° C) followed by rash c vesicles or firm pustules in same stage of development without other apparent cause
- Laboratory Criteria:
  - Culture, PCR, or EM

Case Classification

CDC 2003: Smallpox Plan and Guidelines

- Confirmed: Laboratory confirmed
- Probable:
  - Meets clinical case definition
  - Epidemiological link to another confirmed or probable case
- Suspect
  - Meets clinical case definition, no epidemiological link
  - OR: Atypical clinical presentation, but + epidemiological link to confirmed or probable case
- Contact: < 6 ft (2 m) of a suspected, probable, or confirmed case

Treatment: Cases

CDC 2003: Smallpox Plan and Guidelines

- Quarantined in Type C (Contagious) facility
  - Dedicated ventilation/air conditioning
  - HEPA filtered exhaust or > 100 yds from nearest occupied structure
- Vaccinate all cases (protect misdiagnosed pts)
- Supportive care by vaccinated care givers
  - Gowns, gloves, M 95 masks until vaccine take can be verified.

Management of Contacts
CDC 2003: Smallpox Plan and Guidelines

- Immediate vaccination (or boosting) of all contacts
  - Clinical “take” within three years confers immunity
  - given within 1 week of exposure
  - Most effective if given < 24 hrs p exposure
- Quarantine: Must remain within 20 miles
  - Type R facility
- Household members of contacts:
  - Vaccinate except those c vaccine contraindications
  - Contraindication: Stay outside home without direct contact with people being monitored

Management of Contacts
CDC 2003: Smallpox Plan and Guidelines

- Active surveillance for 18 days from last contact of 14 days from successful vaccination
  - Contact monitors, records T morning and evening
  - Report results by telephone once daily
  - “DOT” desirable if resources available
- T >101° F (38.° C) on 2 successive readings
  - Report to Health Dept, remain in home until transported to Type C or Type X facility

Management of Febrile Contacts

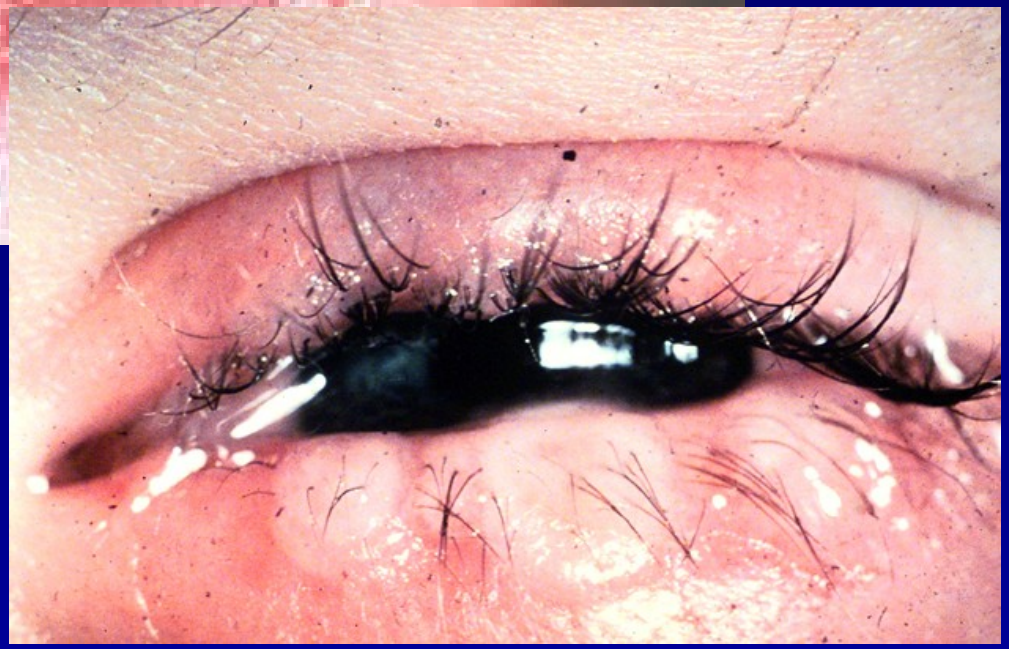
CDC 2003: Smallpox Plan and Guidelines

- Type X facility
- Vaccinate if not already done
- Monitor closely for development of rash
- If rash develops, transfer to Type C facility
- If no rash develops within 5 days and fever due to vaccination or other cause:
  - release to home
  - surveillance for 18 days following last contact with a case or 14 days after successful vaccination.

Multipuncture vaccination

by bifurcated needle

Source: NEJM



Sollico V. Fulginiti MD

Vaccinia: Precautions

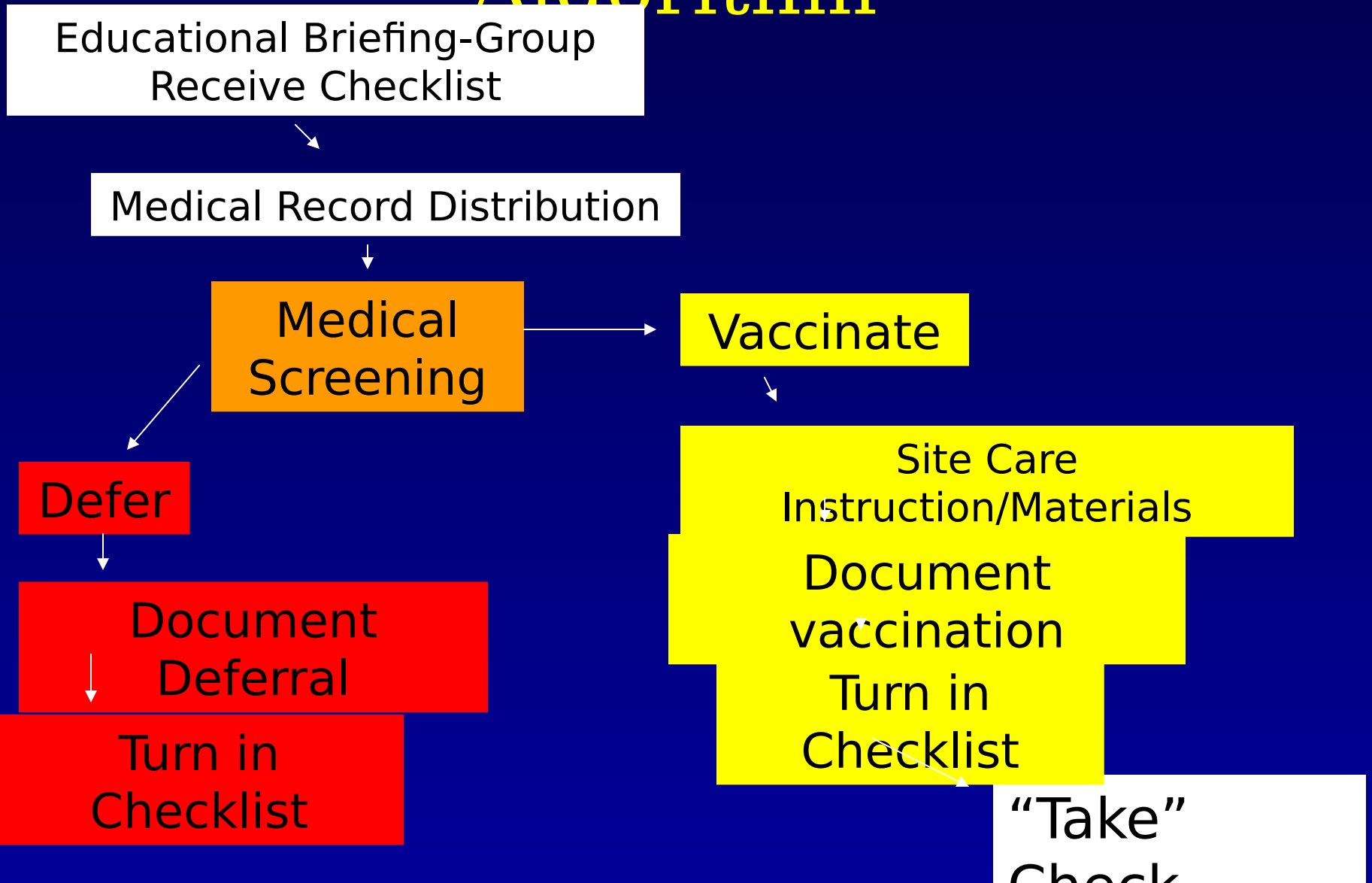
- Infection control measures key to prevent secondary inoculation
  - Vaccinia present at lesion from papule (2-5 d) until scabbed (10-17 d p vaccination)
  - Lesion covered c dressing
    - transparent dressings predispose to local secondary innoculation
    - Strict handwashing after dressing change
  - HCWs: Excluded from care of vaccinia lesions if pregnant, immunocompromised, or with chronic exfoliative dermatoses

Vaccine Contraindications:Non-Contacts

- Immunosupression
  - HIV infection, Humoral or cellular immune deficiencies
  - Organ transplant patients
  - Leukemia/lymphoma/generalized malignancy
  - Alkylating agents/high dose steroid/radiation Rx
- History of atopic dermatitis/eczema
  - Predisposed to eczema vaccinatum even while in remisssion
  - Other exfoliative or extensive skin lesions- psoriasis, burns-, cystic acne-OK if successfully rx'd/inactive
- Conjunctival/corneal diseases (esp c pruritis)
- Pregnancy
- Allergy to vaccine components (polymyxin B, streptomycin, neomycin, TCN)
- History of cardiac or coronary artery disease; multiple coronary risk factors
- HCWs excluded from care of vaccinia lesions: pregnant, immunocompromised, or with atopic dermatitis

***MMWR* 2001;50:RR-10 ; ACIP 21 Oct 2002 Guidelines**

Hospital-based Vaccine Algorithm



Symptoms After Smallpox Vaccination

Day 6-8, “Take Check,” symptoms since vaccination, n = 5,951, Jan-Apr 2003

- Local itching 62% Muscle ache 27%
- Feeling lousy 26% Lymph nodes swell 23%
- Headache 23% Bandage reaction 16%
- Itchy all over 11% Fever (subjective) 6.6%
- Local rash 11% Body rash 2.3%

- Restricted activity 2.4% Took medication 5.0%
- Outpatient visit 1.1% Limited duty 0.3%
- Missed work 0.4% Hospitalized 0.1%

DoD Smallpox Vaccination Program
as of 12 Dec 03

- Noteworthy Events among 526,677 Vaccinees:
  - Encephalitis— 1—recovered
  - Generalized vaccinia— 35, all mild, all recovered
  - Inadvertent infection—Skin: Self—51, Contact—26
  - Inadvertent infection—Eye: Self—11, Contact— 2
  - Contact transfer. Main risks = bed partners, not bandaging.
    - Family—14, intimate contact—6, friend—8, patient—0
  - Vaccinia Immune Globulin (VIG) treatments: Burn-1, eye-1
  - Myo-pericarditis: Suspect—0, probable—67, confirmed—2
  - Eczema vaccinatum: zero Progressive vaccinia: zero
  - HIV+: 10, CD4 counts 300-700, all 'took,' all healed
  - Deaths: 5 Not attributed to vaccine: 4 Undetermined: 1

DoD Smallpox Vaccination Program
Myopericarditis cases

- Myopericarditis:
- First 18 cases: *JAMA* 2003;289:3283-89
  - Onset: 7 to 19 d. Male: 18/18 Age: 21 to 33 y
  - Primary: 18/18 Chest pain: 18/18 ST change: 16/18
  - ↑ Enzymes : 18/18 Abnml echo: 10/18 Recover: 18/18
  - Relative risk: 3.6 for a 30-day interval (95% CI: 3.3, 4.1)
- 35 (67%) available for comprehensive follow-up, 8 ± 6 w.
  - 28 (80%) report complete clinical recoveries
  - 22 normal resting echocardiography
  - 13 normal stress exercise test
  - 2 (6%) persistent non-specific resting EKG changes
- Conclusion: Vaccination appears to increase risk of myopericarditis among adult male primary vaccinees. Most recover promptly.

DoD Smallpox Vaccination Program
Cardiac Ischemia

- Ischemia, admission diagnosis: 18. Onset interval: 2 to 14, 36 d
  - Myocardial infarction-10 (1 fatal), angina-4, atrial fibrillation-2, atherosclerotic coronary vascular disease-2.
  - Admission diagnosis changed to myocarditis: 4 MI, 2 angina cases.
- Expected ischemic admissions, age-adjusted:
  - 14-day window—25, upper 95% CI—30
- Fatality: 55 y/o smoker w/ 3-vessel coronary occlusion, left ventricular hypertrophy, cardiomegaly, no myocarditis.
  - Cardiovascular deaths, Army: average 50 per year.
- Conclusion: Ischemia after smallpox vaccination does not exceed expected level in unvaccinated people in DoD population.

Lesssons Learned: 2003 Smallpox Preparedness Plan

- Careful screening reduces adverse events < or = 1960s levels.
  - VIG needed less frequently than expected.
- Education and screening are rate-limiting steps.
- 3 or 15 jabs yield similar primary “take” rates.
- Clinicians alarmed by first (maculopapular) rashes they saw in vaccinees; decreased with experience.
- Secondary spread of vaccinia: Greatest risk is to bed partners.
- Myopericarditis is greater risk than anticipated, principally male, primary vaccinees in DoD’s experience.

Treatment: Vaccinia Complications

- Eczema vaccinatum
  - VIG 0.6 ml/kg/d pending clinical improvement
- Vaccinia necrosum
  - VIG 0.6 ml/kg/d pending clinical improvement
- Ocular vaccinia
  - Topical opthalmics: idoxuridine, vidaribine
  - VIG contraindicated in keratitis

Antiviral Rx

- Cidofovir
  - Active in vitro vs variola
  - Active in vivo: postexposure prophylaxis, monkeypox model (rhesus macaques)
- Postexposure prophylaxis
  - No guidance for use
- Therapy of cases-variola
  - IND protocol
- Rx vaccinia adverse reactions
  - IND protocol
- Anectdotal report-adjunctive use-ribavirin-vaccinia necrosum (*Clin Infec Dis* 1997;25:911-4)

Pre-Release Vaccination (CDC/DHHS Smallpox Response Plan)

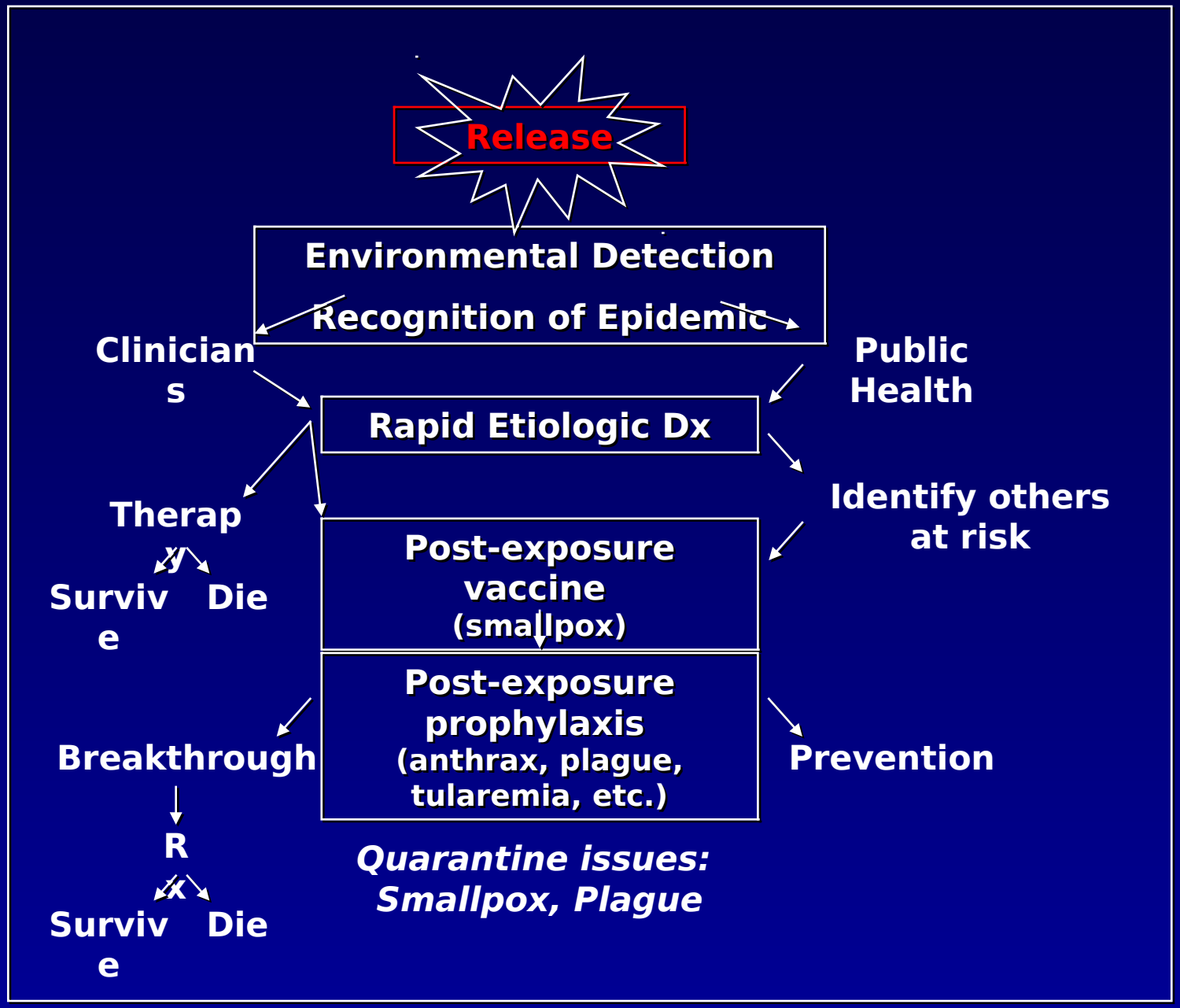
- General public: Not recommended
- Smallpox Response Teams
  - Predesignated by bioterrorism and public health authorities to conduct investigation and follow-up of initial cases
- Designated smallpox healthcare personnel at designated hospitals
- Implementation: Multiple challenges

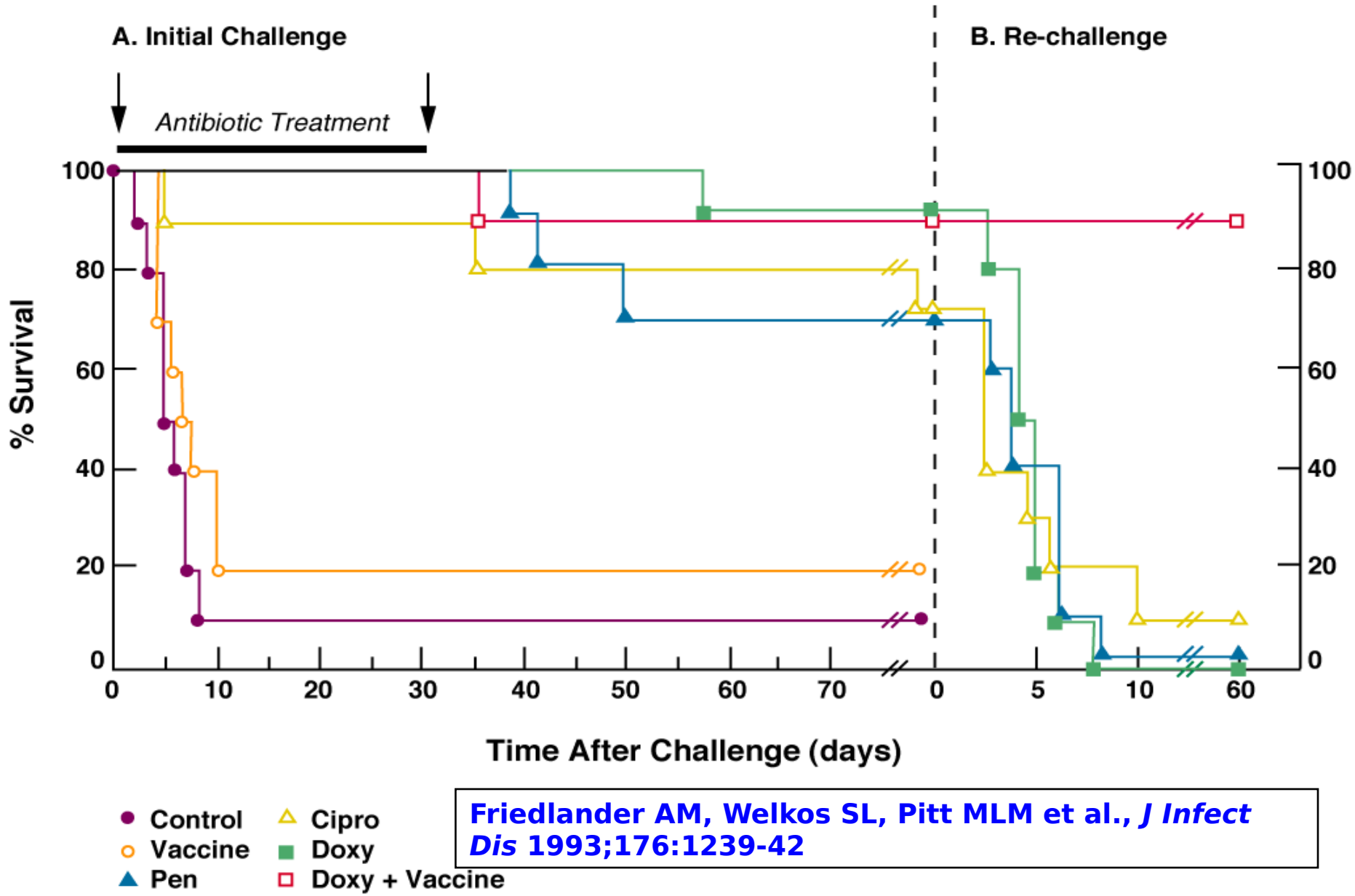
Adverse Event Reporting

- **Vaccine Adverse Event Reporting System (VAERS)**
  - **FDA reviews 100% of adverse-event reports submitted to either FDA or DoD**
  - **Reviewed by independent panel of civilian physicians for 4 years**
  - **Anyone can submit a VAERS Form**
- **DoD requires a VAERS Form submission for:**
  - **Loss of duty 24 hours or longer (≥ 1 duty day)**
  - **Hospitalization**
  - **Suspected vaccine vial contamination**
- **Other submissions encouraged**
- **VAERS Form may be obtained from:**
  - **1-800-822-7967 or www.vaers.org**

Websites

- U.S. Army Medical NBC Defense Information: http://www.nbc-med.org
- CDC Emergency Preparedness Resources: http://www.bt.cdc.gov
- Military Vaccines Website http://www.vaccines.army.mil FBI (suspicious package info): http://www.fbi.gov/pressrel/pressrel01/mail3.pdf
- USAMRIID General Information: http://www.usamriid.army.mil
- Johns Hopkins Center for Civilian Biodefense: http://www.hopkins-biodefense.org
- Infectious Diseases Society of America: http://www.idsociety.org/bt/toc.htm


Release
Environmental Detection
Recognition of Epidemic
Clinicians
Public Health
Rapid Etiologic Dx
Therapy
Survive
Die
Identify others at risk
Post-exposure vaccine (smallpox)
Post-exposure prophylaxis (anthrax, plague, tularemia, etc.)
Breakthrough
Prevention
R
x
Survive
Die
Quarantine issues:
Smallpox, Plague



Friedlander AM, Welkos SL, Pitt MLM et al., *J Infect Dis* 1993;176:1239-42

Postexposure Prophylaxis: Re-challenge (Nonhuman Primates)

(JID 1993;167:1239-42)

Prophylaxis	Ab	Deaths: Rechallenge
Penicillin	Neg	7/7
Ciprofloxacin	Neg	6/7
Doxycycline	Neg	9/9
Doxy + vacc	Pos	0/9

Postexposure Prophylaxis: Nonhuman Primates

(JID 1993;167:1239-42)

Prophylaxis	Anthrax Deaths	P vs. control
Control	9/10	
Vaccine	8/10	>.1
Penicillin	3/10	<.02
Ciprofloxacin	1/9	<.002
Doxycycline	1/10	<.002
Doxy + vacc	0/9	<.0002

Efficacy - Premarketing

- 1962 - 1971 (Premarketing experience)
  - 27 cases of anthrax in high risk industries
  - All cutaneous
  - Only 3/27 had received any vaccine
    - 1 had one dose 7 months prior
    - 2 had two doses, with second dose 2-4 ds. Prior
  - No cases with 3 doses or >7 days since second dose

Independent Scientific Reviews

- **FDA Panel on Review of Bacterial Vaccines & Toxoids, *Federal Register* 1985; 50: pages 51002-117**
- **Armed Forces Epidemiological Board (AFEB), advising DoD, 1994 to present**
- **Cochrane Collaboration, Oxford, *Vaccine* 1998;16:880-4**
- **Working Group on Civilian Biodefense, *JAMA* 1999; 281: pages 1735-45**
- **CDC's Advisory Committee on Immunization Practices (ACIP) (*MMWR* 2000;49(RR-15): pages 1-20)**
- **Anthrax Vaccine Expert Committee (AVEC), 1998 to**

Anthrax Vaccine - Human Trial

- Jan 1955 - March 1959
- 1249 workers in 4 mills
  - 379 Vaccinated
  - 116 Didn’t complete vaccine series
  - 414 Placebo
  - 340 No vaccine or placebo
  - **Brachman, et al, AJPH, 1962;52:632**

Efficacy - Human Trial

- Cutaneous anthrax (21 Cases)
  - 18 either placebo or no vaccine
  - 1 had receive d 2 doses
  - 2 had received 3 doses, but 5-13 months since
  - 92.5% efficacy in protecting against cut. anthrax
- Inhalation anthrax (5 cases)
  - 5 cases received placebo or no vaccine
  - No cases among vaccine recipients

Brachman, et al, AJPH, 1962 ; 52:632

Safety Data Submitted to FDA 1970

- 6,985 subjects (16,500 doses)
  - Mild local reactions (redness < 1 inch in diameter, slight tenderness
    - 5-10% initial series (1-6) doses
    - 3-16% boosters
  - Moderate local reactions (redness of 1-2 inches diameter with itching and tenderness)
    - 1-3%
  - Severe local reactions
    - 1%
  - Systemic reactions (4/16,500)
    - 0.024%

Long-Term Studies

- **Anthrax-Vaccine Recipients Followed for Years**
  - **TAMC-600 Survey (Tripler Army Medical Center)**
  - **Defense Medical Surveillance System (inpatient and outpatient visit surveillance)**
  - **Naval Health Research Center (inpatient and outpatient visit surveillance)**

- **Anthrax-Vaccine Recipients Followed for Decades**
  - **Fort Detrick Multi-Dose, Multi-Vaccine**